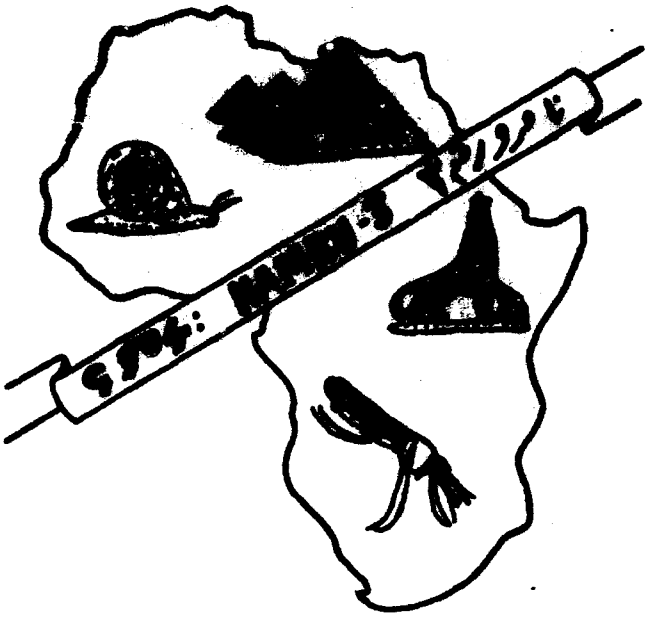

TECHNICAL REPORT

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TREATMENT OF CHRONIC URINARY SALMONELLA CARRIERS

By

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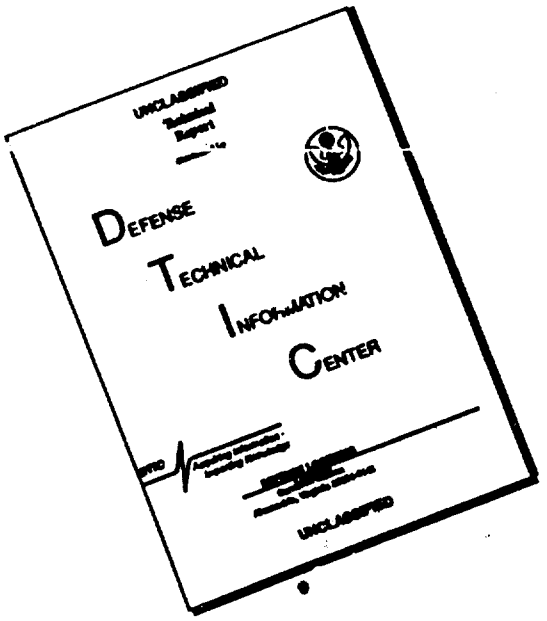

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13. ABSTRACT

Treatment of chronic urinary salmonella carriers with chloramphenicol at a dosage of 50 mg. per kg. body weight for 14 days was unsuccessful in 15 patients. All began to excrete salmonella again soon after completing treatment. All had active urinary schistosomiasis.

A second goup of 14 patients were treated with antimony tartrate or niridazole at a standard dose and 4 weeks of ampicillin at a dosage of 100 mg. per kg. body weight per day. 5 of these 14 patients relapsed but intravenous pyelography revealed that 3 of these 5 patients had advanced irreparably damaged urinary tracts and micturating cystograms showed that the other 2 had an established vesico-ureteric reflux.

Though all 26 patients had a urinary carrier history of 12 months before treatment, all had positive blood cultures for the same organisms.

It is suggested that chronic urinary salmonella carriers in Egypt be thoroughly examined and those with damaged urinary tracts due to schistosomiasis be given the benefit of anti-schistosomal treatment. Further studies are necessary to determine the exact place of prolonged chloramphenicol or ampicillin given alone or with anti-schistosomal treatment in the management of these patients.

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TREATMENT OF CHRONIC URINARY SALMONELLA CARRIERS

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It has long been recognized that chronic urinary salmonella carriers constitute a serious public health problem; these patients are constant potential sources of infection (CHADWICK et al., 1954). At least one large outbreak of typhoid fever among British Service Men in the Suez Canal Zone was traced to a urinary excretor of *S. typhi* (ANDERSON and RICHARDS, 1948).

Treatment of enteric carriers, whether faecal or urinary, is notoriously difficult and reports on the results of treatment contradictory. WOODWARD et al. (1950) reported the failure of curing 4 faecal excretors with large doses of chloramphenicol. DOUGLAS (1950) failed to cure 5 urinary carriers with chloramphenicol while MILLER and FLOYD (1954) from Egypt reported the cure of 10 out of 15 urinary carriers treated with chloramphenicol at a dosage of 3 grammes daily for 10 days. Recently CHRISTIE (1964) and WHITBY (1964) have shown that high doses of ampicillin for long periods may successfully cure chronic typhoid carriers.

The problem in Egypt is even more complicated since the high incidence of urinary salmonella carriers in this country (MILLER, 1950) is closely related to the presence of urinary tract infection with *Schistosoma haematobium* (NEVA, 1949; MILLER and FLOYD, 1954; HALAWANI and BADRAN, 1958; HATHOUT et al. 1966). Furthermore these chronic urinary salmonella excretors often have recurrent phases of bacteraemia when both blood and urine cultures are positive for the same organisms (FARID et al., in press). From 1964 to 1969 we succeeded in studying 40 such patients—that is patients with a urinary carrier history of over 12 months and with repeated blood cultures positive for salmonella.

This paper discusses our experience in the management of these patients.

Materials and methods

Patients

26 male Egyptian farmers aged 4 to 30 years were finally included in the treatment-study. All were ill for over 12 months; 8 were urinary excretors of *S. typhi* and 18 of *S. paratyphi A* and all had repeatedly positive blood cultures for the same organisms. All were excreting live eggs of *S. haematobium* in the urine.

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Naval Department, the Naval Service at large, or the Egyptian Ministry of Public Health.

The authors would particularly like to thank Captain L. F. Miller for helping to initiate this study and for his continued encouragement during its completion.

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Treatment

From 1964 to 1966, 15 of these patients were treated with chloramphenicol 50 mg. per kg. body weight per day for 14 days (Group I). From 1966 to 1968 11 other patients were given oral ampicillin and at the same time received treatment for schistosomiasis. In addition 3 of Group I patients, treated in 1966 and who had relapsed, were retreated according to the new plan making a total of 14 patients receiving both antibiotic and antischistosomal treatment (Group II). 8 of these 14 patients were treated with niridazole 25 mg. per kg. body weight per day for 6 days and 6 received antimony tartrate 0·5 grain per 15 kg. body weight per dose for 12 doses given intravenously twice weekly. At the same time all 14 patients received oral ampicillin 100 mg. per kg. body weight per day for 4 weeks.

Laboratory Investigations

These included complete blood counts, routine urinalysis, and stool examination for ova and parasites. Widal and Brucella agglutination titres were estimated before and after treatment. Blood, urine, and stool cultures were taken twice weekly before treatment, during treatment, and throughout the prolonged follow-up period. All patients were followed-up for 6 to 12 months.

Blood cultures—Blood specimens were cultured on Castaneda-type two phase bottles (CASTANEDA, 1947) and on 10% Ox Bile (KAYE, 1966). 3 ml. blood specimens were introduced into both the 9 ml. Ox Bile and the Castaneda bottles and incubated at 37 C. Subcultures were made from the Ox Bile after 24 hours incubation and if negative repeated at 4 to 6 days. Castaneda bottles were incubated until growth was observed or for a maximum of 21 days before being considered negative. Positive bottles were subcultured on to plating media.

Urine cultures—5 mm. loopfuls of urine were plated directly on selective media. In addition 5 ml. of urine were added to an equal amount of Selenite Broth (Difco) and incubated for 24 hours before plating on the same selective media.

Stool cultures—Swab samples of stool specimens were plated on selective media. The swabs were then placed in Selenite Broth and treated in the same manner as urine specimens.

Plating media employed for all specimens included Bismuth Sulphite Agar, MacConkey Agar, and SS Agar. Isolates possessing cultural and biochemical characteristics of salmonellae were confirmed and identified serologically for "O" and "Vi" antigens in slide agglutination tests.

Pyelography

Plain X-ray films of the bladder region, intravenous pyelography, and micturating cystograms were performed on selected patients.

Results

Treatment.

Group I.—All except 1 of the 15 patients treated with chloramphenicol alone relapsed within the first 3 weeks following treatment. The remaining patient relapsed on the 56th day after treatment. 4 of these 15 patients were urinary excretors of *S. typhi* and 11 of *S. paratyphi A*. Positive blood cultures for the same organisms were obtained after relapse from 10 of these 15 patients. 6 were retreated with chloramphenicol but all relapsed again (Table I).

Group II.—Of the 14 patients treated simultaneously with antimony tartrate or niridazole and with oral ampicillin for 4 weeks 5 relapsed within the first 4 weeks following treatment. 3 of these 5 patients continued to excrete *S. paratyphi A* in the urine, one excreted the organism in the urine and shed it in the blood. The fifth patient continued to excrete *S. typhi* in the urine (Table II). All these patients were followed up for 6

to 12 months after completing treatment. Intravenous pyelography was performed on 13 of these 14 patients. In addition micturating cystograms were performed also on the 5 patients refactory to treatment (Table III).

12 of these 13 patients showed damaged urinary tracts caused by the schistosomiasis. Bladder calcification was present in 6 patients (Nos. 1, 3, 5, 8, 11 and 12). Nodular filling-in defects of the bladder were detected in 3 patients (Nos. 2, 7 and 13) and hydroureter and hydronephrosis of one or both kidneys were present in 4 patients (Nos. 1, 5, 6, and 9). Stricture of one or both ureters with poor dye excretion was

TABLE I. Results of initial chloramphenicol treatment. 6 to 12 Months Follow-up. (Group I)

Patient No.	Age Years	Organisms cultured from blood and urine	Twice weekly urine cultures after treatment	Twice weekly blood cultures after treatment
1	12	*S. typhi*	Positive 3rd day	Positive 21st day
2	12	,,	,, 14th day	,, 40th day
3	13	,,	,, 7th day	,, 10th day
4	21	,,	,, 10th day	Negative
5	13	*S. paratyphi A*	,, 56th day	Positive 56th day
6	21	,,	,, 3rd day	,, 21st day
7	12	,,	,, 10th day	,, 7th day
8	4	,,	,, 7th day	,, 7th day
9	17	,,	,, 7th day	,, 12th day
10	10	,,	,, 3rd day	,, 7th day
11	15	,,	,, 7th day	,, 7th day
12	13	,,	,, 7th day	Negative
13	12	,,	,, 14th day	,,
14	30	,,	,, 21st day	,,
15	13	,,	,, 7th day	,,

N.B.—Repeated stool cultures before treatment and during the follow-up period were negative.

present in 2 patients (Nos. 8 and 10). Vesico-ureteric reflux was present in 2 patients (Nos. 1 and 7, Figure 1). Patient No. 14 had a normal pyelogram and patient No. 4 refused X-ray.

After treatment 6 patients showed improved pyelograms (Nos. 2, 3, 10, 11, 12, and 13). In these patients improvement in bladder contour, resolution of the bladder nodular filling defects, and relief of ureteric strictures with rapid passage of dye occurred

6 patients showed no improvemen (Nos. 1, 5, 6, 7, 8, and 9). 5 of these 6 patients relapsed clinically and bacteriologically following combined anti-schistosomal-antibiotic treatment.

TABLE II. Results of combined anti-schistosomal and ampicillin treatment. 6 to 12 months follow-up. (Group II)

Patient No.	Age years	Organisms cultured from blood and urine	Twice weekly urine cultures after treatment	Twice weekly blood cultures after treatment
1	15	*S. typhi*	Positive 7th day	Negative
2	14	,,	Negative	,,
3	13	,,	,,	,,
4	14	,,	,,	,,
5	29	*S. paratyphi A*	Positive 28th day	Positive 42nd day
6*	22	,,	,, 28th day	Negative
7	13	,,	,, 28th day	,,
8	20	,,	,, 21st day	,,
9*	18	,,	Negative	,,
10*	11	,,	,,	,,
11	13	,,	,,	,,
12	30	,,	,,	,,
13	8	,,	,,	,,
14	20	,,	,,	,,

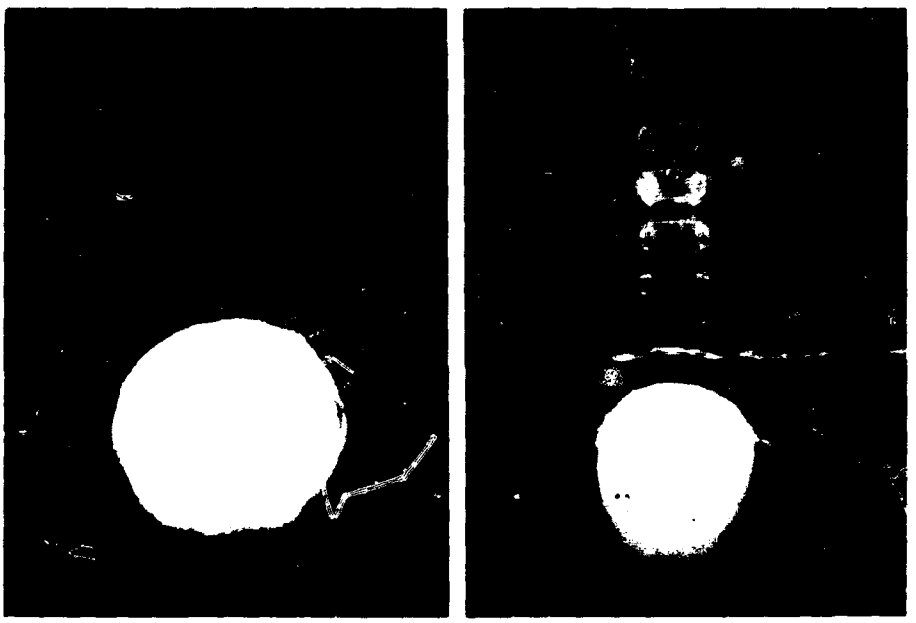
*Had received chloramphenicol 12 months previously and relapsed.

N.B.—Repeated stool cultures before treatment and during the follow-up period were negative.

Side-effects.

No serious side-reactions were experienced with either chloramphenicol or ampicillin. Both antibiotics were effective in controlling the bacteraemia. Within a few days of starting treatment with either chloramphenicol or ampicillin all patients became afebrile and blood and urine cultures became negative for salmonella. As the general condition of the patients improved anti-schistosomal treatment could usually be started.

There were no side-effects with the use of antimony tartrate. Injections were given twice weekly and each intravenous injection was given slowly over a 10 minute period. With niridazole treatment, however, one patient had a profound shock-like syndrome after the first dose and had to be treated with antimony tartrate. Of the 8 patients completing treatment with niridazole 1 had convulsions on the last day of treatment, 1 complained of a severe headache and 5 had marked nausea and vomiting which was only controlled by reducing the total daily dose.



Patient No. 1 Patient No. 7

Micturating cystograms of patients Nos. 1 and 7 showing reflux of 5% sodium iodide outlining left urinary tracts.

TABLE III. Radiological data on the 5 patients refractory to combined anti-schistosomal and ampicillin treatment

Patient No.	Age years	Anti-schistosomal treatment	Intravenous pyelography		Micturating cystogram
			Before treatment	After treatment	
1	14	Niridazole	Hydroureters; hydronephrosis	Resolution of hydroureters and hydronephrosis	Vesico-ureteric reflux
5	29	Niridazole	Hydroureters; hydronephrosis; bladder calcification	No improvement	No reflux
6	21	Antimony tartrate	Hydroureters; hydronephrosis	No improvement	No reflux
7	13	Niridazole	Nodular filling-defects of the bladder	Partial resolution of nodular filling-defects	Vesico-ureteric reflux
8	20	Niridazole	Left hydroureter with stricture	No improvement	No reflux

Discussion

MILLER (1954) 15 years ago working in Egypt reported curing 10 of 15 urinary salmonella carriers with a 10-day course of chloramphenicol even though all his patients had active urinary schistosomiasis. We were not able to confirm this work. All our 15 patients treated with chloramphenicol for 14 days relapsed soon after treatment. All had active urinary schistosomiasis.

HALAWANI and BADRAN (1958) suggested that treatment of urinary schistosomiasis first may increase the response of urinary salmonella carriers to chloramphenicol treatment. HATHOUT et al. (1966) demonstrated a close relationship between urinary schistosomiasis and urinary enteric carriers and showed radiologically that a high percentage of his patients had damaged urinary tracts (HATHOUT et al., 1967).

Schistosomal lesions of the urinary tracts were demonstrated in 12 of 13 patients in Group II receiving anti-schistosomal-antibiotic treatment. 6 of these 13 patients showed improved pyelograms following treatment. None of these relapsed. By contrast the 5 patients who did relapse after treatment showed no radiological improvement after anti-schistosomal treatment. 3 of these 5 patients were over 19 years of age and had advanced obstructive lesions of the urinary tracts. The other 2, though young, had established vesico-ureteric reflux.

Recently FARID et al., (1967; in press) and others (LUCAS et al., 1966) have shown that treatment of urinary schistosomiasis in young patients may result in disappearance of the schistosomal bladder granulomas with relief of obstruction and resolution of the hydronephrosis. It is in these selected young patients that anti-schistosomal treatment, by relieving the obstruction, may help to clear the carrier condition. Further studies are, however, necessary to find out whether anti-schistosomal treatment may not alone be sufficient to cure these patients.

We confirmed WATSON'S (1967) impression that chronic urinary salmonella excretors may also intermittently shed the same organisms into the blood. Though all our patients had a urinary carrier history of 12 months all repeatedly had positive blood cultures too. Chloramphenicol and ampicillin were equally useful in temporarily clearing the blood and urine of salmonella with resultant rapid improvement in the patients' general condition. The value of these drugs in curing the chronic carrier condition has still to be properly assessed. They are probably most useful in curing patients without damaged urinary tracts (HATHOUT et al., 1967).

Summary

Treatment of chronic urinary salmonella carriers with chloramphenicol at a dosage of 50 mg. per kg. body weight for 14 days was unsuccessful in 15 patients. All began to excrete salmonella again soon after completing treatment. All had active urinary schistosomiasis.

A second group of 14 patients were treated with antimony tartrate or niridazole at a standard dose and 4 weeks of ampicillin at a dosage of 100 mg. per kg. body weight per day. 5 of these 14 patients relapsed but intravenous pyelography revealed that 3 of these 5 patients had advanced irreparably damaged urinary tracts and micturating cystograms showed that the other 2 had an established vesico-ureteric reflux.

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It is suggested that chronic urinary salmonella carriers in Egypt be thoroughly examined and those with damaged urinary tracts due to schistosomiasis be given the

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